Identification of these neurons in *Drosophila* awaits definitive identification of a true sex pheromone in this species.

One of the most appealing results of this study are the many similarities between the olfactory systems of organisms separated by hundreds of millions of years of evolutionary time. Olfactory sensory neurons differentially express one of a large family of receptors that recognize multiple odors, and various odors are recognized by more than one receptor, leading to a combinatorial code for potentially hundreds of odors over orders of concentrations. Receptors of similar sensitivities are loosely segregated into stereotyped anatomical regions. Even the classical technique of recording the tuning curves of sensory receptor neurons and pairing them with anatomical and structural data has, in this most molecular of organisms, provided new insights into how the fly "knowses" about its world.

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Smelling Well with a Code in the Nodes

The current renaissance in computational neuroscience is seen particularly clearly in studies of olfaction (Hopfield, 1999; Linster and Cleland, 2001; Laurent et al., 2001). The group of computational neuroscientists trained in the appropriate mathematical techniques and motivated to create neurobiologically realistic neuronal simulations is increasing dramatically, augmented by physicists and mathematicians who see biological questions as a suitably challenging domain for the exercise of their talents. Olfactory processing circuits have proven particularly attractive to many of these converts (Ermentrout and Kleinfeld, 2001). Increased computing power and simulation sophistication are making it a common occurrence for circuit simulations to be used as yet another tool for interpreting data and selecting the most critical future experiments.

It is also readily apparent that the problems solved by the olfactory system are similar to those solved by other sensory systems, including the more familiar sensory modalities of vision and audition (Hildebrand and Shepherd, 1997). To understand olfaction, one confronts questions common to all sensory systems, such as how feature detection, background suppression, and selective attention are implemented, how receptor arrays are mapped onto interneuron populations, and how prior experience modifies sensory processing.

Circuits for early olfactory processing in the locust have yielded a rich harvest of cellular and network responses to odor application, due largely to work by Gilles Laurent and colleagues at CalTech. Two papers in this issue (Bazhenov et al., 2001a, 2001b) provide a particularly elegant example of the creative use of these data to make detailed neuronal and network simulations of early olfactory processing in the locust. These simulations establish the minimal set of cellular and network properties needed to reproduce existing measurements of neuronal response properties in the locust olfactory system. In addition, the simulations are used to explore the effects of manipulating single biophysical variables in the locust early olfactory system in ways not possible with current experimental technique, e.g., changing the density of calcium-activated K^+ channels in a subset of neurons by 50%. The work is also paradigmatic in that it represents a collaboration between physicists and neurobiologists committed to constructing a model tightly constrained by the wealth of available data and able to suggest biologically plausible new experiments.

One of the central findings of the experimental work on locust and honeybee olfactory processing circuitry is an odor-triggered oscillation in the local field potential (LFP) of the antennal lobe. An oscillatory local field potential was first described more than 50 years ago by Lord Adrian in studies on the olfactory bulb of the hedgehog. Spontaneous or odor-triggered LFP oscillations are a universal feature of olfactory processing systems (Gelperin, 1999). Hints as to the computational role of oscillations in olfaction are just beginning to emerge. Previous work by Laurent and coworkers using honeybees suggested that oscillations led to synchronization of interneuron responses, which was critical for discriminating two similar odors but not two very different odors (Stopfer et al., 1997). In a remarkable set of experiments with intact restrained honeybees, antennal lobe network dynamics was altered pharmacologically to eliminate odor-elicited synchronization but maintain average levels of interneuron firing while behavioral measures of odor discrimination were obtained. With synchronization blocked, similar odors were confused while dissimilar odors were discriminated. This work generated great interest as one of a very small set of experiments involving restricted and reversible CNS perturbations with behavioral read out. Similar results indicating the importance of oscillations for odor discrimination have been obtained with block of LFP oscillations in the antennal

lobe analog of a molluscan odor processing circuit in vitro (Teyke and Gelperin, 1999).

The new work of Bazhenov et al. presents a series of network simulations of increasing complexity that explore the roles of fast and slow inhibition and various patterns of connectivity between projection neurons and local inhibitory neurons in molding interneuron response dynamics in the antennal lobe, a region analogous to the mammalian olfactory bulb. As in many cortical areas, there is a population of local inhibitory interneurons whose connectivity and response properties are critical for shaping the response dynamics of the class of projection neurons carrying information to higher integrative centers. The odor-elicited activity of the projection neurons has two robust and reliable features. First, the projection neurons fire in a pattern phase-locked to the odor-elicited oscillation in the LFP. Second, the projection neurons do not fire on every cycle of the LFP oscillation, but rather have an odor-specific firing pattern in which they are active on some cycles but not others, timed by the LFP oscillation. This odor- and cycle-specific pattern of projection neuron firing is the central experimental finding that provided the essential challenge to and validation of the network simulation. What patterns of connectivity and strengths and time scales of inhibitory interactions would endow the network simulation with the essential property of odor-elicited synchronization and odor-specific firing patterns? Guided by prior anatomical work in which patterns of connectivity and cell numbers in the locust antennal lobe were measured, Bazhenov et al. used connectivity patterns in their simulation that maintained the biological ratio of projection neurons and local inhibitory cells. An exemplary feature of their simulation is its adherence to measured biological parameters whenever they are available.

Bazhenov et al. discovered that a critical feature of the simulated network dynamics was the ratio of fast to slow inhibition of the projection neurons by the presynaptic local inhibitory neurons. The presence of two time scales of inhibition is essential to obtain the odor- and cycle-specific patterns of responses by the projection neurons. The ability to change the ratio and strengths of the two forms of inhibition, fast and slow, provided insight into the range of values that allowed responses of simulated projection neurons to closely mimic responses recorded in the biological system. Similarly, the way in which the two classes of interneurons were activated by sensory inputs was manipulated to determine the effects of different connectivity patterns on projection neuron response patterns. A particularly compelling result was obtained in comparisons of projection neuron responses when very similar but not identical patterns of sensory neuron activation of local inhibitory interneurons were used. Differences of a few percent in the overlap of sensory cells onto local inhibitory interneurons were amplified by circuit dynamics in the antennal lobe so that distinct odor-specific interneuron response patterns developed over the course of the several cycles of LFP oscillation induced by odor application. This suggests that very similar odors may need longer stimulus applications to be discriminated than very different odors, which is amenable to experimental test.

A central assumption of the analysis performed by Bazhenov et al. is that the information available to a human observer looking at the patterns of projection neuron spike trains is used by the locust in making decisions about odor identity and odor discrimination. This is a widely shared assumption in the field of sensory coding and in measurements of the information content of neuronal spike trains. This assumption is seldom tested, hence the great interest in the prior experiments in honeybees measuring odor responses before, during, and after perturbing the LFP oscillation in the antennal lobe. The new work identifies several new opportunities for critical circuit perturbations that should degrade odor identification if the locust is extracting information from the antennal lobe in the ways the experimenters think that it is. New work on training locusts with odor cues may make the circuit perturbation experiments previously done with honeybees practical with locusts. Although locust central neurons are much more accessible than honeybee interneurons, the odor learning ability of locusts is only now being documented. Another issue raised by the prior honeybee experiments showing degradation of odor discrimination with antennal lobe desynchronization is: How can the bee do so well at identifying and discriminating dissimilar odors when its antennal lobe projection neurons are desynchronized by application of picrotoxin? Clearly synchronization of projection neuron responses is not critical for all odor categorization computations.

It is well to keep in mind the full range of computations performed by olfactory systems (Gelperin and Hopfield, 2001), for example, the identification of ratios of minor components in an odor mixture used for insect sexual signaling. Computing the number of odor objects represented in a sequence of brief odor samples may involve determination of which components co-vary in fixed proportions. The simulations used by Bazhenov et al. should be able to explore these issues. Odor processing is also altered by prior experience with an odor, whether simply due to previous exposure or by associative learning that an odor predicts a positive or negative consequence. The patterns of action potentials produced by locust projection neurons sharpen up over repeated brief presentations of the same odor, with a memory of prior odor presentations lasting 10 min (Stopfer and Laurent, 1999). In both vertebrate and invertebrate olfactory systems, odor learning alters the way in which odors are represented in the antennal lobe or olfactory bulb. Explorations of these issues in simulations may require addition of neuromodulatory feedback from higher centers onto the simulated antennal lobe. The torrent of recent papers imaging early olfactory processing and odor representations in a variety of species from bees to mice gives promise of specifying in detail how odor learning affects odor representations at the very earliest stages of odor processing (Menzel, 2001; Zufall and Munger, 2001).

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